JACC Vol. 22, No. 3
September 1993:714–9

Effect of Thrombolysis on Acute Mitral Regurgitation During Evolving Myocardial Infarction

Experience From the Thrombolysis in Myocardial Infarction (TIMI) Trial

KENNETH G. LEHMANN, MD, FACC, CHARLES K. FRANCIS, MD, FACC,
FLORENCE H. SHEEHAN, MD,* HAROLD T. DODGE, MD, FACC* AND THE TIMI STUDY GROUP†

New Haven, Connecticut and Seattle, Washington

Objectives. **This study was undertaken to determine whether early successful thrombolysis can reverse infarct-associated mitral valve dysfunction.**

Background. **Mitral regurgitation is a common complication of acute myocardial infarction and has been shown to adversely affect both short- and long-term prognosis. Although anecdotal reports have suggested that reperfusion of the infarct-related artery may restore normal function to the mitral valve, this theory has not been subjected to formal investigation.**

Methods. **Patients with total or partial obstruction of the infarct-related artery received intravenous thrombolytic therapy with either streptokinase or recombinant tissue-type plasminogen activator within 7 h of symptom onset (mean 4.8 h) as part of the Thrombolysis in Myocardial Infarction (TIMI) Phase I trial. Repeat coronary angiography assessed arterial patency at 90 min and 10 days after attempted reperfusion. The presence and severity of mitral regurgitation were determined by contrast ventriculography both before thrombolysis and before hospital discharge.**

Results. **Overall, 21 (16%) of the 132 study patients exhibited mitral regurgitation on either their initial or their predischarge ventriculogram. The proportion of infarct-related arteries found to be patent (TIMI flow grade 2 or 3) was statistically similar in patients with and without mitral regurgitation during each angiographic evaluation period (initial, 90 min and 10 days). Although coronary artery perfusion increased overall during sequential measurement (mean TIMI grade was 0.4 ± 0.6 initially, 1.5 ± 1.3 at 90 min and 2.2 ± 1.0 at 10 days), the pattern of reperfusion observed could not predict an increase or decrease in regurgitant severity (p = NS). Early mitral regurgitation resolved in 57% of patients by 10 days, but this resolution appeared independent of the presence or absence of improved coronary perfusion (60% vs. 50%). The development of new regurgitation during the recovery period (6%) was also unrelated to improved perfusion (7% vs. 4%).**

Conclusions. **Acute mitral regurgitation developing during myocardial infarction shows frequent changes in its presence or severity during the 1st 10 days, appears independent of coronary artery patency both early and late after thrombolysis and cannot be reliably treated by improving arterial perfusion with thrombolytic agents.**

(J Am Coll Cardiol 1993;22:714–9)

One important sequela of acute myocardial infarction is persistent dysfunction of the mitral valve. This complication not only can lead to early sudden death (1) but also has been shown to have a major impact on 1-year mortality (2,3). The past decade has witnessed tremendous growth in the understanding of the mechanisms underlying acute infarction, accompanied by the development of chemical and mechanical techniques designed to abort the process and lessen the extent of necrosis. It is possible that the same processes that lead to myocardial salvage during reperfusion may limit or reverse mitral valve incompetence. Indeed, several case reports have been published that appear to support this theory (4–6); however, more controlled trials have not been reported to date.

The current study examines this hypothesis as part of the Thrombolysis in Myocardial Infarction (TIMI) trial, using the reference standard of contrast left ventriculography for detection and quantitation of mitral regurgitation. Both the patency and perfusion of the infarct-related artery and the presence and severity of regurgitation were measured shortly after presentation and before hospital discharge. These variables were also compared in patients lacking mitral regurgitation who served as a control group. The relation of valvular function to vessel patency over time was evaluated using several different analytic approaches.

From the Division of Cardiology, Yale University School of Medicine, New Haven, Connecticut and *Division of Cardiology, University of Washington School of Medicine, Seattle, Washington. †A complete list of the TIMI Study Group appears in Reference 3. This study was presented in part at the 62nd Scientific Sessions of the American Heart Association, New Orleans, Louisiana, November 1989. It was supported by research contracts and grants from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Manuscript received October 29, 1992; revised manuscript received March 8, 1993, accepted March 10, 1993.

Address for correspondence: Kenneth G. Lehmann, MD, Section of Cardiology (111C), Seattle Veterans Affairs Medical Center, 1660 South Columbian Way, Seattle, Washington 98108.

0735-1097/93/$6.00

Methods

Study population. Patients enrolled in this study were selected from participants in Phase I of the TIMI trial, a multicenter investigation sponsored by the National Heart, Lung, and Blood Institute designed to establish the relative thrombolytic efficacy of intravenous streptokinase and recombinant tissue-type plasminogen activator (rt-PA) during acute myocardial infarction (7). Pretreatment coronary angiography and contrast left ventriculography in the acute phase of infarction were standard requirements of this trial. TIMI eligibility criteria included 1) age <76 years; 2) severe ischemic pain of at least 30-min duration; 3) new or presumably new ≥0.1 mV ST segment elevation in two or more electrocardiographic leads; 4) time interval <7 h between the onset of symptoms and administration of thrombolytic therapy; 5) lack of cardiogenic shock, uncontrolled hypertension or left bundle branch block at presentation; 6) ability and willingness to grant informed consent. Three additional criteria were required for entry into the current study: 7) lack of previous myocardial infarction, cardiac surgery or dilated cardiomyopathy to help exclude preexistent mitral regurgitation; 8) good contrast ventriculograms free of artifactual regurgitation arising from catheter malpositioning or ventricular ectopic activity; 9) repeat coronary angiography and ventriculography before hospital discharge. The latter criterion (predischarge catheterization) was requested of all participants in the TIMI I trial and was performed in 64% of the 206 patients who were otherwise eligible for inclusion in the current study. The 132 patients who satisfied all of the aforementioned requirements form the basis of this report.

Protocol. Each patient was taken to the cardiac catheterization laboratory shortly after presentation, where left ventriculography was performed in a 30° right anterior oblique position. Coronary arteriography was subsequently undertaken, with the infarct-related artery carefully visualized in orthogonal views both before and after administration of intracoronary nitroglycerin. All patients with persistent stenoses in the infarct-related artery of ≥50% diameter reduction underwent randomization to receive either a 1-h infusion of streptokinase (1.5 million U) or a 3-h infusion of rt-PA (80 mg). Repeat coronary injections were performed 90 min after initiation of thrombolytic therapy. Intravenous administration of heparin was started and was continued until predischarge catheterization 8 to 10 days later (7).

Quantitative analysis. All cineangiographic films were sent to the Radiographic Core Laboratory at the University of Washington, Seattle, for quantitative analysis. Anterograde coronary perfusion was assessed in the infarct-related artery at baseline ("initial"), after 90 min of thrombolytic therapy ("90 min") and before hospital discharge ("10 days"). Variables based on contrast left ventriculographic analysis were measured before attempted thrombolysis ("early") and before hospital discharge ("late"). The extent of perfusion was measured using the TIMI grading system: grade 0 = no perfusion; grade 1 = penetration without perfusion; grade 2 = partial perfusion; grade 3 = full perfusion. Endocardial contours were digitized from the left ventriculogram by an experienced observer at end-systole and end-diastole using frames of minimal and maximal area, respectively. Ventricular volumes were computed by the area-length method after compensation for magnification and pincushion distortion (8,9). The extent of akinesia/dyskinesia was determined using the centerline method and was expressed as a percent of the left ventricular contour. Using a sinus beat, mitral regurgitation was graded as "none" if no contrast medium appeared in the left atrium during ventricular injection, "mild" if contrast medium did appear but was of insufficient quantity to completely fill the left atrium and "moderate or severe" if complete atrial opacification occurred. All analyses were performed by observers unaware of the clinical variables.

Data analysis. Average data are expressed as mean values ± SD. Statistical analysis was performed using a two-tailed unpaired *t* test and analysis of variance for continuous variables where appropriate. Categoric variables were analyzed using a chi-square test for 2 × 2 contingency tables and an exact test for 2 × 3 tables (10); $p < 0.05$ was required for statistical significance.

Results

Of the 132 patients enrolled in the study, 16% had mitral regurgitation evident on either their initial or their predischarge contrast ventriculogram. The clinical, hemodynamic and angiographic findings in these 21 patients are shown in Table 1. These variables were compared with those in patients lacking mitral regurgitation (Table 2). A greater proportion of patients exhibiting regurgitation were women ($p < 0.001$), with a higher likelihood of involvement of the left anterior descending coronary artery as the infarct-related artery ($p < 0.05$); however, other variables related to ventricular size, function and filling, as well as enzymatic index of the extent of myocardial necrosis, did not differ significantly between groups.

The temporal pattern of vessel patency (TIMI perfusion grade ≥2) for the infarct-related artery is graphically depicted in Figure 1, grouped into patients exhibiting mitral regurgitation on either ventriculogram (n = 21) and patients with no ventriculographic evidence of regurgitation at any time (n = 111). Before administration of thrombolytic therapy, there was a statistically insignificant trend toward higher arterial patency in patients lacking mitral regurgitation; however, after attempted thrombolysis, even this insignificant trend disappeared, so that the patency rate did not differ between the two groups at 10 days (76% vs. 68%, p = NS).

Further analysis was undertaken to determine whether a change in severity of mitral regurgitation over time was accompanied by a change in perfusion in the infarct-related artery. Figure 2 displays the mean vessel perfusion score in the 16 patients in whom the severity of regurgitation either improved (n = 8) or worsened (n = 8) over the 1st 10 days

Table 1. Clinical, Hemodynamic and Angiographic Characteristics of the 21 Patients With Mitral Regurgitation*

Pt No.	Age (yr)/ Gender	Mitral Regurgitation		Infarct-Related Artery	TIMI Perfusion			EF (%)		LVEDV (ml)		LVEDP (mm Hg)		Dyskinesia (%)		Max CK (IU/liter)	Thrombolytic Agent
		Early	Late		0 min	90 min	10 days	Early	Late	Early	Late	Early	Late	Early	Late		
1	60/M	Mild	Mild	RCA	0	3	3	38	33	221	240	8	10	20	11	1,410	rt-PA
2	59/M	Mild	Mild	LAD	1	0	1	41	41	121	163	25	10	36	37	4,080	SK
3	59/F	Mild	Mild	LAD	2	2	2	51	59	97	102	20	10	27	18	1,396	SK
4	71/F	Mild	Mild	LAD	0	0	3	55	61	105	72	36	30	22	5	5,000	SK
5	65/M	Mild	Mild	LAD	1	2	3	38	46	102	107	20	24	19	12	4,630	rt-PA
6	61/F	Mild	Mod/sev	RCA	0	3	3	51	61	99	106	18	18	0	0	1,990	rt-PA
7	74/F	Mild	None	LAD	1	3	3	37	39	98	106	35	18	37	24	2,835	rt-PA
8	70/M	Mild	None	LAD	0	1	3	53	50	169	183	20	14	18	10	1,705	SK
9	41/M	Mild	None	LAD	0	0	1	54	59	144	131	20	10	13	12	2,136	rt-PA
10	67/F	Mild	None	RCA	0	0	2	56	54	75	98	12	14	0	4	892	SK
11	55/M	Mild	None	LAD	1	3	3	39	28	227	179	15	8	15	21	1,978	rt-PA
12	60/M	Mild	None	LAD	0	2	3	39	39	161	181	34	16	40	36	3,553	SK
13	36/M	Mild	None	RCA	0	1	0	42	38	173	116	22	16	1	0	1,596	SK
14	68/F	Mod/sev	None	RCA	0	1	3	46	55	132	133	12	6	8	5	523	rt-PA
15	51/F	None	Mild	LAD	1	3	3	38	45	103	89	26	18	37	25	3,468	rt-PA
16	33/M	None	Mild	RCA	0	0	2	58	42	173	197	16	20	0	14	7,744	SK
17	64/M	None	Mild	LAD	0	0	3	46	33	137	131	25	27	33	32	1,206	SK
18	66/M	None	Mild	RCA	0	0	0	62	58	140	133	6	15	6		541	SK
19	55/M	None	Mild	RCA	0	1	1	71	64	108	87	14	14	0	3	606	SK
20	37/M	None	Mild	LCx	0	3	3	51	49	127	132	20	14	0	0	4,770	rt-PA
21	74/F	None	Mod/sev	RCA	1	3	2	49	56	62	89	30	20	2	0	2,615	rt-PA

*Clinical and catheterization data for all patients with mitral regurgitation on either ventriculogram. Dyskinesia = percent of chords that are akinetic or dyskinetic; Early = within 7 h of symptom onset; EF = ejection fraction; F = female; LAD = left anterior descending coronary artery; Late = approximately 10 days after infarction; LCx = left circumflex coronary artery; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; M = male; Max CK = maximal serum creatine kinase value; Mod/sev = moderate or severe; TIMI Perfusion = Thrombolysis in Myocardial Infarction perfusion grade (baseline [0 min], after 90 min of thrombolytic therapy [90 min] and before hospital discharge [10 days]); Pt = patient; RCA = right coronary artery; rt-PA = intravenous recombinant tissue-type plasminogen activator; SK = intravenous streptokinase.

after infarction. Although on average, perfusion did improve with time (overall mean TIMI grade was 0.4 ± 0.6 initially, 1.5 ± 1.3 at 90 min and 2.2 ± 1.0 at 10 days), it did so to a similar extent in each group, so that mean perfusion grades did not differ significantly between groups at any given point in time. Similarly, temporal changes in left ventricular performance, assessed by ejection fraction, end-diastolic volume or extent of akinesia/dyskinesia, could not predict changes in regurgitation severity.

Finally, patients were separated according to whether or not thrombolytic therapy produced an improvement in arterial perfusion at 10 days (TIMI grade ≥2) relative to the initial angiogram. As shown in Figure 3 (top), in approximately half of patients with initial mitral regurgitation, the regurgitation resolved before the final ventriculographic study; however, this rate of resolution was similar in those with or without improved coronary perfusion (60% vs. 50%). Similarly, the likelihood of developing mitral regurgitation in patients with a competent valve initially (Fig. 3, bottom) was independent of improvement in perfusion (7% vs. 4%).

Discussion

It is widely recognized that mitral regurgitation can develop during the course of acute myocardial infarction (11). The previously published frequency of this complication varies with the techniques used for detection but ranges from 10% to 55% (2,11–14). We recently reported a 13% prevalence of mitral regurgitation within the 1st 7 h of symptom onset (3). In our series, this valvular lesion was more common in patients with anterior infarction, but it did not correlate with peak creatine kinase levels or early ventricular dilation. Moreover, the early presence of mitral regurgitation was the strongest predictor of cardiovascular mortality, with relative risks of 7.3 at 10 days (95% confidence interval [CI] 1.4 to 38.4) and 12.2 at 1 year (95% CI 3.5 to 42.0). It is logical to hope that timely restoration of valvular competence may improve this otherwise poor prognosis.

Optimal restoration of valvular function requires an understanding of the underlying pathogenesis. Unfortunately, the mechanisms involved in this complication appear to be multifactorial. At one extreme is frank papillary muscle rupture, leading to immediate hemodynamic compromise and, often, to a quick demise (1). At the other is a more subtle disruption of the complex architecture that comprises the valve and its supporting subvalvular apparatus (15). Further controversy exists as to whether mitral valve incompetence is largely a problem of restricted papillary muscle and leaflet motion, leading to incomplete valve closure, or to

Table 2. Comparison of Patients With and Without Mitral Regurgitation

	Mitral Regurgitation	
	Present (n = 21)	Absent (n = 111)
Age (yr)	58 ± 12	55 ± 10
Men (%)	62	90*
Infarct-related artery (%)†		
RCA	43	50
LAD	52	40
LCx	5	10
Perfusion		
0 min	0.4 ± 0.6	0.6 ± 0.9
90 min	1.5 ± 1.3	1.7 ± 1.2
10 day	2.2 ± 1.0	2.0 ± 1.3
EF (%)		
Early	48.3 ± 9.2	50.2 ± 9.4
Late	48.1 ± 10.7	51.4 ± 9.3
LVEDV (ml)		
Early	132 ± 43	145 ± 38
Late	132 ± 43	151 ± 41
LVEDP (mm Hg)		
Early	20.7 ± 8.4	19.1 ± 10.1
Late	15.8 ± 6.1	15.0 ± 6.0
Extent of akinesia/dyskinesia (%)		
Early	15.9 ± 14.5	11.3 ± 12.8
Late	13.5 ± 12.2	8.9 ± 11.7
Max CK (IU/liter)	2,604 ± 1,844	2,330 ± 1,665
Thrombolytic agent (%)		
SK	48	57
rt-PA	52	43

*$p < 0.001$. †$p < 0.05$. Values presented are mean values ± SD unless otherwise indicated. Abbreviations as in Table 1.

exaggerated leaflet movement beyond the line of closure, producing valve prolapse (15).

The classic interventional approach to mitral valve dysfunction in this setting has been surgical replacement or repair, usually in conjunction with coronary artery bypass procedures. Uncontrolled series have suggested a survival benefit over that of medical treatment alone (4,16–18), although perioperative mortality can range up to 41% (4). Because of this high surgical risk, an effective alternative approach to restoring valve competency would clearly be preferable.

In theory, reestablishing perfusion in the infarct-related artery early in the course of an evolving myocardial infarction might restore the functional integrity of the mitral valve without surgery. Several investigators have reported anecdotal evidence that supports this concept. Shawl et al. (5) were apparently able to reverse moderate and severe acute mitral regurgitation in five patients undergoing emergency coronary angioplasty during infarction, as evidenced by a significant improvement in pulmonary capillary wedge pressure after reperfusion. Follow-up contrast ventriculography at a mean of 35 months revealed no mitral regurgitation in three of four patients tested (5). This same technique was

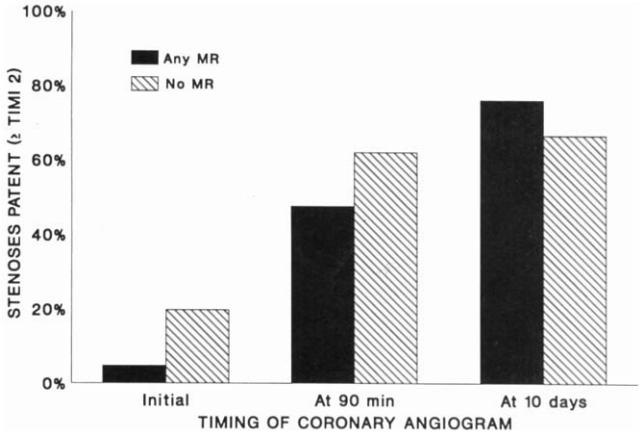
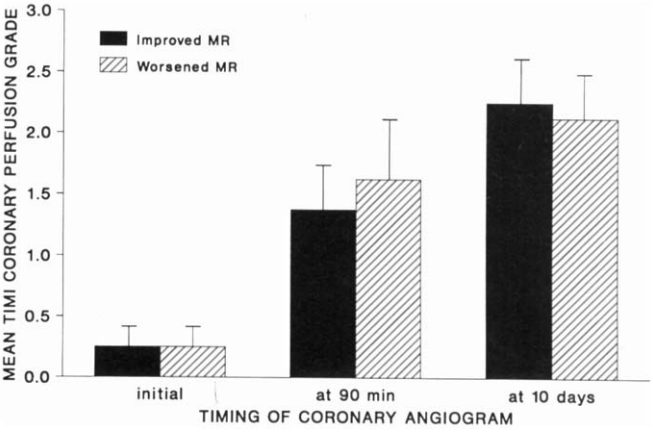


Figure 1. Infarct-related artery patency over time subgrouped by the presence or absence of angiographic mitral regurgitation (MR). Patients are grouped according to those with regurgitation observed on their early or late ventriculogram (any MR) and those without regurgitation evident on either study (no MR). All differences were statistically nonsignificant. ≥TIMI 2 = Thrombolysis in Myocardial Infarction flow grade 2 or greater.

successfully applied by Heuser et al. (6) to three patients with severe regurgitation, two of whom were in cardiogenic shock at the time of the procedure. The mean pulmonary wedge pressure decreased from 34 to 10 mm Hg after successful coronary dilation in these three patients, with no clinical heart failure or auscultatory evidence of mitral regurgitation observed at 1-year follow-up. Recently, Hickey et al. (4) retrospectively reported on nine patients undergoing angioplasty within 24 h of the onset of infarction. Six of the nine patients experienced complete resolution of regurgitation after successful reperfusion.

The favorable results noted in these uncontrolled reports are not reflected in our data. Although a different technique was used in our study to establish reperfusion (intravenous

Figure 2. Average Thrombolysis in Myocardial Infarction (TIMI) perfusion grade of infarct-related artery over time in the 16 patients with mitral regurgitation (MR) that either decreased (improved MR) or increased (worsened MR) in severity from the early to the late ventriculogram. Error bars denote standard error.



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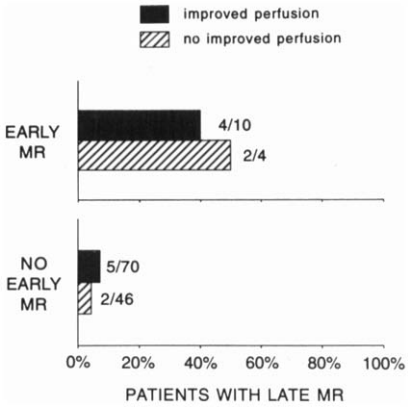

Figure 3. Prevalence of late mitral regurgitation (MR) in patients with or without early regurgitation, based on whether coronary flow improved in the infarct-related artery between the baseline and the 10-day coronary angiogram. Ratios (to the right of each bar) represent the number of patients with late regurgitation in the numerator, with the total number of patients in each group in the denominator.

thrombolytic therapy vs. coronary angioplasty), the time to achieving vessel patency was similar. The severity of regurgitation, however, was typically less in our study group. Our results show no statistical difference in vessel patency after thrombolysis in patients with or without mitral regurgitation. In addition, vessel patency could not predict progression or regression of the severity of valve dysfunction over the 1st 10 days after infarction. Similar results were obtained when coronary perfusion grade was used as a nondichotomous and potentially more physiologic marker of reperfusion. Improved coronary perfusion after attempted thrombolysis did not affect the frequency of late mitral regurgitation. Finally, our data documented spontaneous resolution of mitral dysfunction in 57% of patients, with no apparent relation to reperfusion. This phenomenon has not been addressed in previous reports.

Study limitations. Several potential limitations of our study should be noted. Most important, although the current study reports the largest experience to date, the total number of patients included is small. Second, thrombolytic therapy was initiated a mean of 4.8 h after symptom onset; earlier treatment could possibly alter the results obtained. Third, of all 206 TIMI I patients who represented potential candidates for this study on their initial hospital day (3), 74 (36%) were ultimately excluded because they did not receive an adequate repeat contrast ventriculogram before discharge. When considering only the 27 patients with initial mitral regurgitation, the proportion excluded was even higher (48%). Stated reasons given for exclusion in the latter subgroup consisted of in-hospital death in three, patient refusal in two, physician refusal in two and technical/logistic difficulties in six. Therefore, caution is advised in the generalized application of our findings to patients who do not exactly match this select group of patients with acute infarction. The fourth limitation relates to the 10-day time period between attempted thrombolysis and reassessment of mitral valve function. It is possible that some of the vessels documented as patent on the late angiogram may have had reperfusion after the critical period needed for myocardial preservation. Alternatively, the 10-day delay before reassessment may have been too short to allow total recovery of residual myocardial function after infarction.

Conclusions. Despite these limitations, the findings from this study support several conclusions. 1) Mitral regurgitation is a common complication of acute myocardial infarction, with frequent changes in its presence and severity during the 1st 10 days after infarction. 2) Vessel patency both early and late after attempted thrombolysis appears similar in patients with and without mitral regurgitation. 3) Neither progression nor regression of mitral regurgitation appears to be influenced by changes in perfusion in the infarct-related artery. We hope that other approaches can be devised in the future to favorably influence the ominous natural history of infarct-associated mitral valve dysfunction.

We are indebted to Victor Froelicher, MD and Nathan Wong, PhD for their editorial review, to the Maryland Medical Research Institute for assistance in data analysis and to Julie Werton for manuscript preparation.

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